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Use of early T lymphocyte activation-1/osteopontin modulators for modulating a type-1 immune response in humans for treating cancer, AIDS, allergy, bacterial arthritis, granulomatous disorder, glomerulonephritis

Patent Assignee: CHILDRENS MEDICAL CENT (CHIL-N); DANA FARBER CANCER INST INC (DAND)

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Patent Family (7 patents, 91 & countries)

Patent Number	Kind	Date	Application Number	Kind	Date	Update	Type
WO 2000063241	A2	20001026	WO 2000US10340	A	20000417	200101	B
AU 200043575	A	20001102	AU 200043575	A	20000417	200107	E
BR 200009791	A	20020108	BR 20009791	A	20000417	200208	E
			WO 2000US10340	A	20000417		
EP 1175223	A2	20020130	EP 2000923454	A	20000417	200216	E
			WO 2000US10340	A	20000417		
JP 2003517284	W	20030527	JP 2000612329	A	20000417	200344	E
			WO 2000US10340	A	20000417		
MX 2001010332	A1	20020901	WO 2000US10340	A	20000417	200370	E
			MX 200110332	A	20011012		
AU 773350	B2	20040520	AU 200043575	A	20000417	200462	E

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Patent Details

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WO 2000063241	A2	EN	120	14		
National Designated States,Original	AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
Regional Designated States,Original	AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
AU 200043575	A	EN			Based on OPI patent	WO 2000063241
BR 200009791	A	PT			PCT Application	WO 2000US10340
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EP 1175223	A2	EN			PCT Application	WO 2000US10340

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Regional Designated States,Original	AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2003517284	W	JA	129		PCT Application	WO 2000US10340
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Alerting Abstract WO A2

NOVELTY - Use of Eta (early T lymphocyte activation)-1/osteopontin (Opn) modulators for modulating a type-1 immune response in a subject.

DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

1. enhancing (M1) production of type-1 immune response associated cytokine by an immune cell, involves contacting the cell with an Eta-1/Opn stimulatory modulator;
2. down regulating (M2) production of a type-2 immune response associated cytokine by an immune cell, involves administering a Eta-1/Opn inhibitory modulator;
3. stimulating (M3) IL(interleukin)-12 production or inhibiting IL-10 production by a macrophage, involves contacting the macrophage with Eta-1/Opn stimulatory modulator or Eta-1/Opn inhibitory modulator, respectively;
4. modified tumor cells comprising irradiated tumor cells transduced with Eta-1/Opn;
5. a biosynthetic immunomodulatory molecule (I) comprising a IL-12 stimulatory component or IL-10 inhibitory component, and a first biomodular component, forming a molecule which modulates an immune response;
6. a biosynthetic immunomodulatory molecule comprising a IL-12 stimulatory component or IL-10 inhibitory component, a calcium/apatite binding domain and a heparin domain;
7. an isolated nucleic acid molecule (II) comprising nucleic acid sequences which encode the above mentioned immunomodulatory molecules;
8. an expression vector (III) comprising (II);
9. a host cell (IV) comprising (III);
10. producing (I) which involves culturing (IV) under conditions such that (I) is produced; and
11. a pharmaceutical composition comprising (I).

ACTIVITY - Antibacterial; virucide; antiparasitic; antifungal; cytostatic; anti-HIV; antiallergic; immunomodulator; antibacterial; immunosuppressive; antiarthritic; antirheumatic; neuroprotective; nephrotropic; ophthalmological; antitumor; vulnerary.

MECHANISM OF ACTION - Type-1 or type-2 immune response modulator i.e. by modulating IL-12 and IL-10 production by immune cells; gene therapy. The biological activity of Eta-1/Opn was tested in mice. Eta-1^{-/-} mice were infected in the right eye with 4x10⁶ plaque forming units (PFU)

herpes simplex virus type-1 (HSV-1) (KOS strain) and challenged five days later in the left footpad with 1×10^5 PFU of UV-inactivated HSV-1 (KOS). Eta-1^{-/-} (Opn^{-/-}) mice infected by HSV-1 (4×10^6 PFU via the cornea) fail to develop a significant delayed type hypersensitivity (DTH) response after footpad challenge with 10^5 pfu HSV-1 in contrast to the strong DTH response of Eta-1^{+/+} (Opn^{+/+}) controls. Eta-1^{-/-} and control mice (Eta-1^{+/+}) were subjected to ocular challenge with virus. Eta-1^{-/-} mice failed to develop significant HSK within 2 weeks after corneal inoculation with HSV-1 in contrast to the severe HSK developed within this period by control littermates (Eta-1^{+/+}) (i.e. 65% of control Eta-1^{+/+} mice developed herpes simplex keratitis (HSK)). Similar results were obtained when the experiment was repeated using BALB/cBgamaJ mice and CB-17 mice in addition to Eta-1^{-/-} and Eta-1^{+/+} mice. Furthermore skewing of the cell numbers in Eta-1/Opn knockout mice after challenge with HSV-1 was diminished compared to control mice in which the increase of CD8⁺ cells is consistent with a Th-1 response. Although cells from the draining lymph nodes of virus-infected Eta-1^{-/-} and Eta-1^{+/+} mice respond equally well to HSV-1 according to [³H]-thymidine incorporation after viral restimulation in vitro, they differed conspicuously according to their cytokine profiles. Cells were isolated and restimulated with HSV-1 (KOS) as described above. Supernatants were harvested 48 h later and IL-10 and IL-12 p40 cytokine levels were measured by sandwich ELISA using OptIEA antibody sets. IL-4 was measured after stimulation of draining lymph node cells by plate-bound anti-CD3. Cells from Eta-1^{-/-} mice produced high levels of IL-10 and IL-4 but markedly reduced levels of IL-12 compared with Eta-1^{-/-} controls. Splenic macrophages from virus-infected Eta-1^{+/+} but not Eta-1^{-/-} mice continued to produce IL-12 ten days after infection. In contrast with the sterile granulomatous response, IFN-gamma levels were not reduced in Eta-1^{-/-} mice after HSV-1 viral function, consistent with an IL-12-independent pathway to IFN-gamma production that may depend on virally induced IFN-alpha/beta production. Moreover expression of IL-2 by lymph node and spleen T lymphocytes from Eta-1^{-/-} and Eta-1^{+/+} littermates in response to immobilized antibody to CD3 was indistinguishable between the C57BL/6x129/SV Eta-1^{-/-} and C57BL/6xEta-1^{+/+} mice. These cytokine profiles suggest that Eta-1/Opn expression normally may imprint the *in vivo* ratio of IL-12 and IL-10 cytokines that dictates a type-1 immunity.

USE - For potentiating a type-1 immune response in a subject which involves culturing immune effector cells from a subject in the presence of Eta-1/Opn stimulatory modulator and then administering the cultured cells to the subject such that type-1 immune response is potentiated. Eta-1/Opn stimulatory modulators are useful for treating burn-associated sepsis, bacterial infection, viral infection, parasitic infection, mycoplasma infection, fungal infection, cancer, immunodeficiency disorders, AIDS, bone marrow transplant-related immunodeficiency, chemotherapy-related immunodeficiency and allergy. The Eta-1/Opn inhibitory modulators are useful for treating bacterial arthritis, granulomatous disorder, glomerulonephritis, rheumatoid arthritis, multiple sclerosis, herpes simplex keratitis, and autoimmune disease. (I) is used for modulating an immune response which involves modulating cytokine secretion, chemotaxis regulation, regulation of haptotaxis, and regulation of cell spreading (claimed). (I) is useful in biasing an immune response towards a delayed type hypersensitivity (DTH) response i.e., towards type-1 immunity. It is also useful for wound healing, enhancement of the immune response and in treatment of granulomatous disease. The nucleic acids encoding (I) are useful in gene therapy techniques for treating the above mentioned disorders.

Technology Focus

BIOTECHNOLOGY - Preferred Method: Modulating type-1 immune response by a Eta-1/Opn

modulator in humans, involves potentiating a type-1 immune response by administering a Eta-1/Opn stimulatory modulator or downregulating a type-1 immune response in a patient by administering a Eta-1/Opn inhibitory modulator. The method further involves monitoring a type-1 immune response by determining the level of a detectable indicator of the type-1 response and further comprises comparing the level of the detectable indicator to a control. The Eta-1/Opn modulator is preferably, a human Eta-1/Opn polypeptide, a biologically active fragment of an Eta-1/Opn polypeptide, an isolated nucleic acid molecule which encodes an Eta-1/Opn polypeptide or an isolated nucleic acid molecule which encodes an biologically active fragment of an Eta-1/Opn polypeptide. Alternately, the Eta-1/Opn modulator is a compound which specifically binds to an Eta-1/Opn, a compound which specifically binds an Eta-1/Opn target molecule, a compound which specifically modulates the activity of an Eta-1/Opn polypeptide or a compound which specifically modulates the activity of an Eta-1/Opn target molecule. Preferably the Eta-1/Opn is an antibody that specifically binds Eta-1/Opn or (I). The Eta-1/Opn polypeptide has at least 90% identity to a polypeptide having a fully defined amino acid sequence of 314 amino acids (S2) as given in the specification. The nucleic acid molecule encoding Eta-1/Opn as 90% identity to a fully defined sequence of 945 nucleotides (S1) as given in the specification. The biologically active fragment of Eta-1/Opn consists essentially of an IL-12 stimulatory domain or an IL-10 inhibitory domain of Eta-1/Opn. The IL-12 stimulatory domain comprises an amino acid sequence between 65-160 amino acids in length and has 90% identity to amino acids 71-168 of (S2). The IL-10 inhibitory domain comprises an amino acid sequence between 65 and 160 amino acids in length and is 90% identical to amino acids 169-266 of (S2). In (M1), the immune cells (macrophages, dendritic cell, T cell, B cell, monocyte or a neutrophil of humans) are contacted with the modulator in vivo or ex vivo such that the type-1 immune response associated cytokines IL-2, IL-12 and interferon-gamma (IFN-gamma) production is enhanced or type-2 immune response associated cytokines such as IL-4, IL-5, IL-6 and IL-10 production is downregulated. The modified tumor cells are further transduced with GM-CSF (granulocyte macrophage - colony stimulating factor). Preferred Immunomodulatory Molecule: The IL-12 stimulatory component of (I) is derived from Eta-1/Opn and is 90% identical to amino acids 71-168 of (S2) or comprises amino acids 71-168 of (S2). The IL-10 inhibitory component of (I) is derived from Eta-1/Opn and is 90% identical to amino acids 169-266 of (S2) or comprises amino acids 169-266 of (S2). It comprises a first biomodular component such as a signal peptide, a calcium/apatite domain or a heparin binding domain. Additionally it comprises a second biomodular component.

Title Terms /Index Terms/Additional Words: EARLY; LYMPHOCYTE; ACTIVATE; MODULATE; TYPE; IMMUNE; RESPOND; HUMAN; TREAT; CANCER; AID; ALLERGIC; BACTERIA; ARTHRITIS; DISORDER; GLOMERULONEPHRITIS

Class Codes

International Patent Classification					
IPC	Class Level	Scope	Position	Status	Version Date
C12N-015/09			Main		"Version 7"
A61K-0031/711	A	I	L	R	20060101
A61K-0035/26	A	I	L	R	20060101

A61K-0038/00	A	I	L	R	20060101			
A61K-0038/17	A	I		R	20060101			
A61K-0038/19	A	I		R	20060101			
A61K-0045/00	A	I	L	R	20060101			
A61K-0048/00	A	I	L	R	20060101			
A61P-0013/12	A	I	L	R	20060101			
A61P-0017/00	A	I	L	R	20060101			
A61P-0017/02	A	I	L	R	20060101			
A61P-0019/00	A	I	L	R	20060101			
A61P-0019/02	A	I	L	R	20060101			
A61P-0025/28	A	I	L	R	20060101			
A61P-0027/02	A	I	L	R	20060101			
A61P-0029/00	A	I	L	R	20060101			
A61P-0031/04	A	I	L	R	20060101			
A61P-0031/10	A	I	L	R	20060101			
A61P-0031/12	A	I	L	R	20060101			
A61P-0031/18	A	I	L	R	20060101			
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A61P-0033/02	A	I	L	R	20060101			
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A61P-0037/00	A	I	L	R	20060101			
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A61P-0037/08	A	I	L	R	20060101			
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A61P-0043/00	A	I	L	R	20060101			
A61P-0007/00	A	I	L	R	20060101			
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C07K-0014/52	A	I		R	20060101			
C07K-0016/24	A	I		R	20060101			
C12N-0015/09	A	I	F	R	20060101			
C12N-0005/10	A	I	L	R	20060101			
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A61K-0035/26	C	I	L	R	20060101			
A61K-0038/00	C	I	L	R	20060101			

A61K-0038/17	C	I		R	20060101			
A61K-0038/19	C	I		R	20060101			
A61K-0045/00	C	I	L	R	20060101			
A61K-0048/00	C	I	L	R	20060101			
A61P-0013/00	C	I	L	R	20060101			
A61P-0017/00	C	I	L	R	20060101			
A61P-0019/00	C	I	L	R	20060101			
A61P-0025/00	C	I	L	R	20060101			
A61P-0027/00	C	I	L	R	20060101			
A61P-0029/00	C	I	L	R	20060101			
A61P-0031/00	C	I	L	R	20060101			
A61P-0033/00	C	I	L	R	20060101			
A61P-0035/00	C	I	L	R	20060101			
A61P-0037/00	C	I	L	R	20060101			
A61P-0039/00	C	I	L	R	20060101			
A61P-0043/00	C	I	L	R	20060101			
A61P-0007/00	C	I	L	R	20060101			
C07K-0014/435	C	I		R	20060101			
C07K-0016/18	C	I		R	20060101			
C12N-0015/09	C	I	F	R	20060101			
C12N-0005/10	C	I	L	R	20060101			

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Chemical Indexing

Chemical Fragment Codes (M1):

01 M905 M423 M430 M710 M781 M782 N135 P210 P220 P241 P330 P421 P423 P431
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RA00NS-N RA00NS-T 93605-D 93605-M 93605-N 93605-T

02 M905 M423 M430 M710 M781 M782 N135 P210 P220 P241 P330 P421 P423 P431
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RA00H3-N RA00H3-T 184616-D 184616-M 184616-N 184616-T

04 M905 M423 M710 N135 Q233 RA00GT-N 200757-N 200799-N

Chemical Fragment Codes (M6):

05 M905 P210 P220 P241 P330 P421 P423 P431 P434 P440 P450 P633 P723 P831

P922 P942 Q233 Q505 R515 R521 R627 R637 R639

Specific Compound Numbers: RA00NS-D; RA00NS-M; RA00NS-N; RA00NS-T; RA012P-D; RA012P-M; RA012P-N; RA012P-T; RA00H3-D; RA00H3-M; RA00H3-N; RA00H3-T; RA00GT-N

Derwent Chemistry Resource Numbers: (Linked) 93605-D; 93605-M; 93605-N; 93605-T; 105730-D; 105730-M; 105730-N; 105730-T; 184616-D; 184616-M; 184616-N; 184616-T; 200757-N; 200799-N; 93605-CL; 93605-NEW; 105730-CL; 105730-NEW; 184616-CL; 184616-NEW; 200757-CL; 200757-NEW

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31/711(R,I,M,JP,20060101,20051220,C,L) A61K-35/26(R,I,M,JP,20060101,20051220,A,L)

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31/711(R,I,M,JP,20060101,20051220,C,L) A61K-35/26(R,I,M,JP,20060101,20051220,A,L)

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C12N-5/10(R,I,M,JP,20060101,20051220,C,L)

Brazil

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Assignee: CHILDRENS MEDICAL CENT (CHIL-N)

DANA FARBER CANCER INST INC (DAND)

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CANTOR H

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Related Publication: WO 2000063241 A (Based on OPI patent)

Current IPC: A61K-31/711(R,I,M,JP,20060101,20051220,A,L) A61K-

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C12N-5/10(R,I,M,JP,20060101,20051220,C,L)

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Publication Date: 20020130

**VERFAHREN UND ZUSAMMENSETZUNGEN ZUR MODULIERUNG DER
IMMUNANTWORT**

**METHODS AND COMPOSITIONS FOR MODULATING AN IMMUNE RESPONSE
PROCEDES ET COMPOSITIONS DE MODULATION D'UNE REPOSE
IMMUNITAIRE**

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GB

Language: EN

Application: EP 2000923454 A 20000417 (Local application)

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Designated States: (Regional Original) AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT
LU LV MC MK NL PT RO SE SI

Original IPC: A61K-38/17(A) A61K-48/00(B) A61P-37/02(B) C07K-14/47(B) C12N-5/10(B)
C12N-15/12(B) G01N-33/50(B)

Current IPC: A61K-31/711(R,A,I,M,JP,20060101,20051220,A,L) A61K-
31/711(R,I,M,JP,20060101,20051220,C,L) A61K-35/26(R,I,M,JP,20060101,20051220,A,L)
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 C12N-5/10(R,I,M,JP,20060101,20051220,C,L)

Original Abstract:

The present invention features new approaches for modulating immune responses. In particular, the invention features methods for modulating type 1 immune responses in a subject using modulators of Eta-1(early T lymphocyte activation-1)/osteopontin. Exemplary methods feature methods of treating infections, immune disorders and diseases, autoimmune disorders and diseases, various immunodeficiencies and cancer. Also provided are biosynthetic immunomodulatory molecules that include functional domains derived from Eta-1/osteopontin. Preferred biosynthetic immunomodulatory molecules include an IL-12 stimulatory domain derived from Eta-1/osteopontin or an IL-10 inhibitory domain derived from Eta-1/osteopontin. The immunomodulatory molecules of the present invention are capable of biasing an immune response in a subject towards a type 1 immune response. Accordingly,therapeutic uses are disclosed which are based on the biosynthetic immunomodulatory molecules of the present invention.

Japan

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Application: JP 2000612329 A 20000417 (Local application)

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Related Publication: WO 2000063241 A (Based on OPI patent)

Original IPC: A61K-31/711(-) A61K-48/00(-) C12N-15/09(A) A61K-35/26(B) A61K-38/00(B)

A61K-45/00(B) A61P-7/00(B) A61P-13/12(B) A61P-17/00(B) A61P-17/02(B) A61P-19/00(B)

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A61P-31/12(B) A61P-31/18(B) A61P-33/00(B) A61P-33/02(B) A61P-35/00(B) A61P-35/02(B)
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C12N-5/10(B)
Current IPC: A61K-31/711(-) A61K-48/00(-) C12N-15/09(A) A61K-35/26(B) A61K-38/00(B)
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C12N-5/10(B)

Mexico

Publication No. MX 2001010332 A1 (Update 200370 E)

Publication Date: 20020901

Assignee: CHILDRENS MEDICAL CENT (CHIL-N)

DANA FARBER CANCER INST INC (DAND)

Inventor: ASHKAR S

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Language: ES

Application: WO 2000US10340 A 20000417 (PCT Application)

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Priority: US 1999129772 P 19990415

Related Publication: WO 2000063241 A (Based on OPI patent)

Current IPC: A61K-31/711(R,I,M,JP,20060101,20051220,A,L) A61K-
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C12N-5/10(R,I,M,JP,20060101,20051220,C,L)

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METHODS AND COMPOSITIONS FOR MODULATING AN IMMUNE RESPONSE
PROCEDES ET COMPOSITIONS DE MODULATION D'UNE REPOSE
IMMUNITAIRE

Assignee: (*except US*) CHILDREN'S MEDICAL CENTER CORPORATION, 300 Longwood Avenue, Boston, MA 02115, US **Residence:** US **Nationality:** US (CHIL-N)

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(*only US*) ASHKAR, Samy, Apartment 606, 12 Stoneholm Street, Boston, MA 02115, US **Residence:** US **Nationality:** LB

(*only US*) WEBER, Georg, 163 Bellingham Road, Chestnut Hill, MA 02647, US **Residence:** US **Nationality:** --

(*only US*) GLIMCHER, Melvyn, - **Residence:** US **Nationality:** --

(*only US*) CANTOR, Harvey, - **Residence:** US **Nationality:** --

Inventor: ASHKAR, Samy, Apartment 606, 12 Stoneholm Street, Boston, MA 02115, US **Residence:** US **Nationality:** LB

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GLIMCHER, Melvyn, - **Residence:** US **Nationality:** --

CANTOR, Harvey, - **Residence:** US **Nationality:** --

Agent: HANLEY, Elizabeth, A., Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109, US **Language:** EN (120 pages, 14 drawings)

Application: WO 2000US10340 A 20000417 (Local application)

Priority: US 1999129772 P 19990415

Designated States: (National Original) AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

(Regional Original) AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

Original IPC: C07K-14/00(A)

Current IPC: A61K-31/711(R,A,I,M,JP,20060101,20051220,A,L) A61K-

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Original Abstract:

The present invention features new approaches for modulating immune responses. In particular, the invention features methods for modulating type 1 immune responses in a subject using modulators of Eta-1(early T lymphocyte activation-1)/osteopontin. Exemplary methods feature methods of treating infections, immune disorders and diseases, autoimmune disorders and diseases, various immunodeficiencies and cancer. Also provided are biosynthetic immunomodulatory molecules that include functional domains derived from Eta-1/osteopontin. Preferred biosynthetic immunomodulatory molecules include an IL-12 stimulatory domain derived from Eta-1/osteopontin or an IL-10 inhibitory domain derived from Eta-1/osteopontin. The immunomodulatory molecules of the present invention are capable of biasing an immune response in a subject towards a type 1 immune response. Accordingly, therapeutic uses are disclosed which are based on the biosynthetic immunomodulatory molecules of the present invention.

L'invention concerne de nouvelles approches pour la modulation de reponses immunitaires.

L'invention concerne notamment des procedes de modulation de reponses immunitaires de type 1 chez un individu, a l'aide de modulateurs d'Eta-1 (activation precoce de lymphocyte T-1)/osteopontine. A titre d'exemple, on peut citer des procedes portant sur des techniques de

traitement d'infections, de troubles et maladies immunitaires, de troubles et maladies auto-immuns, de plusieurs immunodeficiences et du cancer. L'invention porte également sur des molécules biosynthétiques immunomodulatrices comprenant des domaines fonctionnels dérivés de l'Eta-1/ osteopontine. Des molécules biosynthétiques immunomodulatrices comprennent un domaine stimulateur d'IL-12, dérivé de l'Eta-1/ osteopontine ou un domaine inhibiteur d'IL-10, dérivé de l'Eta-1/ osteopontine. Les molécules immunomodulatrices de l'invention peuvent, chez un sujet, faire pencher une réponse immunitaire vers une réponse immunitaire de type 1. Des utilisations thérapeutiques correspondantes, fondées sur les molécules biosynthétiques immunomodulatrices de l'invention, sont également décrites.

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